

Metabolic/Genetic Newborn Screening Program In Tennessee



Guide for Practitioners

State of Tennessee Department of Health

Maternal and Child Health

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www2.state.tn.us/health/mch/genetics.htm

A program administered by the Tennessee Department of Health (Maternal and Child Health & Laboratory Services) with the assistance of hospitals, primary care providers, endocrinologists, genetic and sickle cell centers from across the state.

I. Tennessee Law

Tennessee Code Annotated (TCA 68-5-401) Part 4 – Newborn Testing – Metabolic Defects

The general assembly hereby declares that as a matter of public policy of this state and in the interest of public health, every newborn infant shall be tested for phenylketonuria, hypothyroidism, galactosemia and other metabolic/genetic defects that would result in mental retardation or physical dysfunction as determined by the department, through rules and regulations duly promulgated.

II. Excerpts taken from Rules and Regulations (complete rules and regulations available upon request)

Chapter 1200-15-1-.01 Tests. The Department of Health will designate the prescribed effective screening tests and examinations which will be performed on the blood samples submitted in accordance with 1200-15-1-.02 for the detection of metabolic/genetic disorders in newborns. Tests are to be conducted for Biotinidase Deficiency, Congenital Adrenal Hyperplasia (CAH), Congenital Hypothyroidism, Galactosemia, Hemoglobinopathies, Homocystinuria, Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl CoA Dehydrogenase (MCAD) Deficiency, Phenylketonuria (PKU), and other metabolic/genetic tests as designated by the Department of Health. Results of the Newborn Hearing Screening, if conducted, are to be submitted in conjunction with the blood sample procedure for the detection of disorder in accordance with 1200-15-1-.02.

- (1) Exemption for religious beliefs. Nothing in this part shall be construed to require the testing of or medical treatment for the minor child of any person who shall file with the department a signed, written statement that such tests or medical treatment conflict with such person's religious tenets and practices, affirmed under penalties of perjury pursuant to T.C. A. 68-5-403. The newborn screening refusal form provided by the State should be completed and retained in the medical record for the period of time defined by the hospital or provider policy.
- (2) Failure to have a child tested for the genetic/metabolic disorders is a Class C misdemeanor. Reporting of hearing screening is not to be construed as mandatory testing, therefore, failure to have a child tested for hearing loss will not be considered a misdemeanor pursuant to T.C.A. 68-5-404.

Chapter 1200-15-1-.02 Institutions Responsible For Test For Newborn Infants

- (1) The following persons or institutions shall be responsible for having tests made on newborn infants:
 - a) Every chief administrative officer of a hospital and the attending physician in each instance shall be responsible for submitting a specimen of blood to the State of Tennessee Laboratory, State Department of Health, in a manner as directed by the department. This sample shall be collected before newborn infants are discharged from the nursery, regardless of age.
 - b) Every chief administrative officer of a hospital and the attending physician shall direct every parent, guardian, or custodian to bring the infant, if the infant was initially screened before twenty-four (24) hours of age, back to the hospital or to a physician or the nearest local health department to be rescreened for Biotinidase Deficiency, Congenital Adrenal Hyperplasia (CAH), Congenital Hypothyroidism, Galactosemia, Hemoglobinopathies, Homocystinuria, Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl CoA Dehydrogenase (MCAD) Deficiency, Phenylketonuria (PKU), and other metabolic/genetic tests as designated by the Department of Health within twenty-four to forty-eight (24-48) hours after birth. In the case of a premature infant, and infant on parenteral feeding or any newborn treated for an illness, who is not discharged from the nursery in a timely manner, the sample should be collected not later than the seventh (7) day of age.
 - c) Any healthcare provider(s) of delivery services in a non-hospital setting shall be responsible for submitting a specimen of blood to the State of Tennessee Laboratory, or directing every parent, guardian, or custodian to bring the infant, between twenty-four and forty-eight (24-48) hours of age, to a hospital, physician or local health department to be screened for Biotinidase Deficiency, Congenital Adrenal Hyperplasia (CAH), Congenital Hypothyroidism, Galactosemia, Hemoglobinopathies, Homocystinuria, Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl CoA Dehydrogenase (MCAD) Deficiency, Phenylketonuria (PKU), and other metabolic/genetic tests as designated by the Department of Health.
 - d) Any parent, guardian, or custodian residing in Tennessee, of an infant born in Tennessee, outside a Tennessee health care facility and without assistance of a health care provider, shall between twenty-four to forty-eight (24-48) hours of the birth of said infant, present said infant to a physician or local health department for testing for the purpose of detecting Biotinidase Deficiency, Congenital Adrenal Hyperplasia (CAH), Congenital Hypothyroidism, Galactosemia, Hemoglobinopathies, Homocystinuria, Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl CoA Dehydrogenase (MCAD) Deficiency, Phenylketonuria (PKU), and other metabolic/genetic tests as designated by the Department of Health.
 - e) The original blood specimen shall be collected between twenty-four and forty-eight (24-48) hours of age. Repeat blood specimens shall be collected before two (2) weeks of age.
 - f) Every chief administrative officer of a hospital in a hospital that performs physiologic newborn hearing screening shall be responsible for reporting the results of the newborn hearing screening test performed prior to discharge from the health care facility. Results of the hearing screening are to be reported to the Department of Health on the form designated for newborn screening blood spot collection or a similar form designated by the department.

III. Hospital Responsibility

A. Completion of the Newborn Screening Form

- Collection forms are available from the local Health Department
- It is important to fill out all information on the Newborn Screening collection form completely and accurately.
- Adoption Cases: **Do Not** put birth mothers information on the form, list either adoptive parents, adoption agency or lawyer. Also write ADOPTION CASE on the collection form. If a specimen needs to be repeated, a letter will be sent using the information listed on the form.
- Death of a Newborn: When a newborn has expired, fax Maternal and Child Health (MCH) follow-up the child's name, birth date, mother's name and the date infant expired. MCH will close the case so mother will not receive letters requesting a repeat specimen. Fax # (615) 262-6458

B. Obtain a Satisfactory Specimen

- A satisfactory specimen is: Drops of whole blood applied evenly and allowed to soak through the filter card and can be seen clearly with no white showing through on either side. Preferably these spots should be large enough to punch at least 6 1/8 inch discs with no white areas.
- Recommended techniques are available upon request. All Tennessee birthing hospitals/facilities and health departments were provided with a newborn screening video, "Let's Do it Right the First Time". The video demonstrates collection procedures and reviews the diseases screened for by the State of Tennessee.
- An unsatisfactory specimen of a newborn with one of the disorders can cause a possible delay in diagnosis and treatment. A specimen can be considered unsatisfactory for several reasons, including quantity insufficient, blood did not soak completely through filter paper, specimen was contaminated or arrived in a plastic bag. A complete list of descriptions for unsatisfactory specimens is available upon request.
- Transfused/Premature/Sick - Newborns who have been transfused prior to collection of newborn screening need to be screened for PKU, CAH and CH, 4 days after transfusion (filter paper to the State Laboratory). Galactosemia, MSUD, MCAD Deficiency, Homocystinuria, Biotinidase Deficiency and analytes tested on Tandem Mass Spectrometry (MS/MS) will need to be re-screened 10 days after transfusion (filter paper to the State Laboratory). The hemoglobin will also need to be repeated 3 months after transfusion, (microvette tubes to Meharry Medical Center). If possible, get a specimen for the newborn screen prior to transfusion, even if the infant is <24 hrs of age, the hemoglobin and biotinidase enzyme is accurate at < 24 hrs of age and will not need to be repeated if results are normal.

C. Parent Education and Pamphlets

Chapter 1200-15-1-.03 Phenylketonuria (PKU), Galactosemia, Congenital Hypothyroidism and Congenital Adrenal Hyperplasia Pamphlet

The chief administrative officer of each hospital shall order the distribution of a pamphlet on Biotinidase Deficiency, Congenital Adrenal Hyperplasia (CAH), Congenital Hypothyroidism, Galactosemia, Hemoglobinopathies, Homocystinuria, Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl CoA Dehydrogenase (MCAD) Deficiency, Phenylketonuria (PKU), and other metabolic/genetic tests as designated by the Department of Health, to every parent, guardian, or custodian of an infant screened for these conditions. The pamphlet, distributed by the Department of Health, educates and prepares the family for newborn screening testing on their infant. If an infant's screen was collected earlier than twenty-four (24) hours after birth and discharged home, the healthcare facility must review the information on the back of the pamphlet with parents, which requires them to present infant to pediatrician or health department within 24-48 hours for repeat screening. The pamphlet will have a perforated page that may be signed by the parent and placed in the medical record as documentation that the pamphlet was provided.

Pamphlets are available upon request.

IV. State Laboratory and Maternal and Child Health Newborn Screening (NBS) Follow-up Section Responsibilities

The Laboratory performs tests on all specimens, reports results to both provider and the hospital of collection listed on the NBS form. Presumptive positives for diseases are immediately reported to MCH follow-up. MCH contacts providers and tertiary centers about presumptive positives, and follows up to ensure patient has confirmatory testing, diagnosis and treatment when necessary. MCH also informs the parent and provider by letter of repeat specimen needed due to presumptive positive for disease, unsatisfactory specimen, transfusion, specimens collected at <24 hrs of age or possible hemoglobin trait.

V. Weekend and Holiday Calls

When the results of a specimen are abnormal, the lab repeats the test in duplicates. Anytime a critical presumptive positive is identified on Friday and needs to be repeated, the lab personnel will come in on Saturday to complete the test. Results will be called to MCH who will contact the provider listed on the newborn screening form and the on call personnel with the appropriate Genetic Center or Endocrinologist. On any holidays greater than 3 days, lab personnel will come in to perform testing, specimens will not go longer than 3 days without being tested.

VI. Primary Care Provider Responsibilities for Follow-up

When the laboratory receives specimens, they are separated according to the age of infant and assigned a Tennessee Department of Health Number (TDH#) before tests are performed. The specimen is handled at the state lab for 2-4 days, not including mailing time.

- A. Specimens Within Normal Limits (WNL)—Reports of normal specimens are mailed within 7 working days from receipt of specimen to provider listed and hospital of collection. No follow-up from the provider is needed, although providers are responsible for making sure their patient has had a newborn screen, reviewed and interpreted results with respect to blood transfusion and diet status. Provider is also responsible for informing parent/guardian of the results.
- B. Unsatisfactory Specimens—Medical Technologists closely examine each specimen for quality and quantity before performing tests. When a specimen is identified as unsatisfactory, the lab notifies the provider and hospital of collection by mail the next working day. MCH also notifies the provider and parents by mail, and requests a repeat specimen to be obtained. It is the responsibility of the parents and provider once notified to obtain a repeat specimen. Specimens are mailed to the state laboratory; a second unsatisfactory specimen at this point can cause a costly delay in diagnosis and treatment.
A description of unsatisfactory specimens is available upon request.
- C. Process for Presumptive Positive for Disease—The laboratory reports a presumptive positive result to MCH as soon as it has been determined, generally within 24-48 hours after the specimen is received. MCH notifies the provider listed on the newborn screening form by telephone and fax to initiate confirmatory testing, follow-up, and treatment of the patient. MCH also notifies the appropriate Endocrinologist, Genetic or Sickle Cell Center. Results will be mailed to provider and hospital of collection when other tests are completed, within 7 days from receipt of specimen. Remember, this is a screening program and further testing will need to be performed prior to diagnosis and treatment.
- D. Exceptions—When MCH and/or the physician are unable to contact/locate an infant for repeat testing due to unsatisfactory or abnormal results, the local health department will be contacted to assist in locating the infant.

VII. List of Endocrinologist, Genetic and Sickle Cell Centers

A. Pediatric Endocrinologists

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| •T.C. Thompson Children's Clinic
Division of Pediatric Endocrinology
Chattanooga (423) 778-6405 | •UT Memphis
Division of Pediatric Endocrinology
Memphis (901) 572-5096 |
| •ETSU
Pediatric Endocrinology
Johnson City (423) 439-7320 | •Children's Hospital
Department of Pediatric Endocrinology
Knoxville (865) 541-8541 |
| •Endocrine Clinic
Memphis (901) 763-3636 | •Vanderbilt University
Department of Pediatric Endocrinology
Nashville (615) 322-7427 |
| •Jackson Pediatric Center, Endocrinology
Jackson (731) 664-9928 | |

B. Genetic/Metabolic Centers

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| •University of Tennessee
Developmental and Genetics Center
Knoxville (865) 544-9030 / 800-325-3894 | •Vanderbilt University Medical Center
Division of Genetics
Nashville (615) 322-7601 |
| •University of Tennessee Memphis
Division of Medical Genetics
Memphis (901) 448-6595 | |

C. Satellite Genetic Centers

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| •East Tennessee State University
Medical Genetics Center
Johnson City (423) 439-8541 | •T. C. Thompson Children's Hospital
Division of Genetics
Chattanooga (423) 778-6112 |
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D. Hematology Centers

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| •T.C. Thompson Children's Hospital
Pediatric Hematology
Chattanooga (423) 778-7289 | •University of Tennessee
Developmental and Genetics Center
Knoxville (865) 544-9030/1-800-325-3894 |
| •Meharry Medical College
Meharry Sickle Cell Center
Nashville (615) 327-6763 | •St. Jude Children's Research Hospital
Pediatric Hematology Center of Memphis
Memphis (901) 495-5670 |

VIII. Metabolic/Genetic Disorders

Disorder Incidence Genetics	Defect	Clinical Symptoms (untreated)	Screening Method	Normal Values	Goals of Screening	Pitfalls of Screening										
Phenylketonuria (PKU) 1/14,000 AR Screening: 1968	Enzyme defect (phenylalanine hydroxylase);increased phenylalanine/phenylketones	Mental retardation Seizures	Elevated phenylalanine (plasma)	<4mg% (If on oral/IV protein/amino acid nutrition, or catabolic)	Identify all infants with phe elevations >4mg%. Assess for therapy before day 14	Inadequate oral/IV protein/amino acid intake										
Congenital Hypothyroidism (CH) 1/3,000 Sporadic AR for hormone Dysgenesis Screening: 1980	Insufficient production of thyroxine due to absent, dysfunctional or ectopic thyroid gland (Primary CH) or to defective TSH secretion by the pituitary (Secondary CH)	Most newborns show none. Jaundice, constipation, coarse facies/ tongue, delayed skeletal maturity, posterior fontanelle, bradycardia, hypothermia	Elevated TSH When pituitary is normal indicates absent or hypo-functioning thyroid gland	<24hrs old=Inconclusive 1-7 Days old Normal = <33μU/ml Borderline = 33-55μU/ml Positive = >55μU/ml 8 days-6months old Normal = <13μU/ml Positive = >13μU/ml	To identify all infants with primary CH and initiate therapy by day 14 of life	Early samples inconclusive due to TSH surge at birth. TSH screen only identifies Primary CH. Some (VLBW) infants with CH display delayed TSH rise										
Hemoglobinopathy 1/350 African Americans AR Screening: 1988	Abnormal Hb (homozygous SS, doubly heterozygous SC, or heterozygous (AS, AC)	Sickle cell disease Associated sepsis, pain crises, pneumonia, anemia, gallstones, splenic enlargement etc.	Isoelectirc focusing, with HPLC or cellulose acetate electrophoresis for confirmation	Hemoglobin = FA pattern	Identify infants with sickle cell disease for case management; identify infants with trait conditions for genetic counseling	Abnormal hemoglobins must be confirmed. RBC transfusion affects results; screen before transfusion										
Galactosemia 1/53,000 (classical) 1/6,000 (variants) AR Screening: 1992	Enzyme defect (transferase) Elevation of galactose and galactose metabolites	<u>Classical</u> : Sudden death (E. coli sepsis); jaundice/hepatomegaly, acidemia, cataracts, mental retardation <u>Variants</u> : milder	Elevated total Galactose in blood RBC based assay (Enzyme screened in specified situation only; RBC based)	Total galactose = <15mg% with enzyme present Reliable when on lactose or galactose in diet	Identify all infants with classical galactosemia, prevent death, and begin diet Immediately Identify all treatable variant forms	Test not reliable on non-lactose/ IV intake, or post RBC transfusion										
Congenital Adrenal Hyperplasia (CAH) 1/19,000 AR Screening: 2000	Enzyme defect in cortisol and aldosterone synthesis. Leads to high ACTH, over secretion of adrenal androgens, and virilization of genitalia. Death from circulatory collapse and salt loss (salt wasting form)	Virilized female genitalia, males not apparent. Vomiting, circulatory collapse, hyponatremia, and hyperkalemia as early as 5 days of life	Elevated 17α-hydroxy-Progesterone (17-OHP)	<table><tr><th>Weight</th><th>Value</th></tr><tr><td><1250gms</td><td><135 ng/ml</td></tr><tr><td>≥1250gms- <1750gms</td><td><90 ng/ml</td></tr><tr><td>≥1750gms- <2250gms</td><td><65 ng/ml</td></tr><tr><td>≥2250gms</td><td><50 ng/ml</td></tr></table>	Weight	Value	<1250gms	<135 ng/ml	≥1250gms- <1750gms	<90 ng/ml	≥1750gms- <2250gms	<65 ng/ml	≥2250gms	<50 ng/ml	Identify all infants with the salt wasting form, 21 hydroxylase deficiency and treat within first week of life. Correct gender assignment in affected females	Early samples inconclusive due to placental 17-OHP. Screening only identifies 21-Hydroxylase form (90% of cases)
Weight	Value															
<1250gms	<135 ng/ml															
≥1250gms- <1750gms	<90 ng/ml															
≥1750gms- <2250gms	<65 ng/ml															
≥2250gms	<50 ng/ml															
Biotinidase Deficiency 1/61,000 AR Screening: 2003	Decrease in biotinidase activity which is needed to free biotin from protein which is required for carboxylases to function properly. When carboxylase is unable to perform their normal functions, altering fat, carbohydrate and protein metabolism, harmful by-products collect in the body	Hypotonia, seizures, coma, tachypnea, stridor, alopecia, conjunctivitis and dermatitis	Biotinidase Enzyme Activity	≥ 11 eru (enzyme response units)	Identify all infants with deficient biotinidase activity	Severity of symptoms and age of onset can vary False negative test results may occur with the use of sulfonamides, repeat filter paper 5 days after sulfonamides discontinued.										

Disorder Incidence Genetics	Defect	Clinical Symptoms (untreated)	Screening Method	Normal Values	Goals of Screening	Pitfalls of Screening
Maple Syrup Urine Disease (MSUD) 1/230,000 AR Screening: 2004	Enzyme defect or deficiency which is needed for metabolism of leucine, isoleucine and valine, amino acids. Life threatening complications may occur due to accumulation of derivatives of above amino acid	Maple syrup odor of urine/sweat. Poor feeding, high pitched cry, vomiting, mental retardation hyper-tonia or hypotonia, convulsions and/or coma	Elevated Leucine and Valine Levels	Leucine < 375 µMol/L Valine < 325 µMol/L	Identify all infants with elevated leucine levels. Assess need for diet and cofactor therapy and begin immediately	Inadequate oral/IV protein/amino acid intake can delay rise in leucine levels. Infant receiving hyperalimentation may have mildly elevated leucine levels.
Medium Chain Acyl-CoA Dehydrogenase (MCAD) 1/12,000 AR Screening: 2004	Deficiency of the enzyme MCAD, which is necessary for the breakdown of certain fatty acids leading to the accumulation of Acyl-CoA derivatives of fats in the liver and the brain	Triggered during periods of fasting. Hypoglycemic, lethargy, vomiting and/or liver malfunction. Viral illnesses that limit food intake may cause symptoms to occur	Elevated Octanoylcarnitine levels	C8 <0.40 µMol/L	Identify all infants with elevated Octanoylcarnitine levels. Assess need for therapy with low fat diet and carnitine; begin treatment immediately	Confirmation may require analysis of urine organic acid, Acyl carnitine profile and DNA studies
Homocystinuria 1/340,000 AR Screening: 2004	Reduced activity of cystathionine beta synthase, which is required for the conversion of homocysteine to cystathionine and cysteine, needed for proper growth and development	Mental retardation, seizures, thrombosis and dislocated lens	Elevated Methionine levels	Methionine < 100 µMol/L	Identify all infants with elevated methionine levels. Assess and initiate diet and cofactor treatment immediately	Inadequate oral/IV protein/amino acid intake can cause methionine to rise slowly.
Amino Acid Disorders AR Screening: 2004	defect in amino acid metabolism caused by a specific defect in the biosynthesis of one of the enzymes	Hypotonia, hypothermia, poor feeding, persistent vomiting, developmental delays, damaged to vital organs, seizures or coma. The effect of the disorder will depend on the age at which symptoms occur	Elevated metabolites using MS/MS related to specific disorder.	Dependent on specific disorder.	Identify all infants with elevated metabolite levels. Assess need for diet and cofactor therapy and begin immediately	Inadequate oral/IV protein/amino acid intake can delay rise in amino acid levels. Infant receiving hyperalimentation may have mildly elevated levels.
Organic Acid Disorders AR Screening: 2004	Defect in protein metabolism where an essential enzyme is absent or malfunctioning causing accumulation of organic acids in blood and urine	Vomiting, metabolic acidosis, ketosis, hyperammonemia, lactic acidosis, hypoglycemia, failure to thrive, hypotonia, global developmental delay, sepsis, hematological disorders and ultimately death. The effect of the disorder will depend on the age at which symptoms occur	Elevated metabolites using MS/MS related to specific disorder.	Dependent on specific disorder.	Identify all infants with elevated metabolite levels. Assess need for diet and cofactor therapy and begin immediately	Confirmation may require analysis of urine organic acids, blood Acyl carnitine profiles and enzymatic studies.

Disorder Incidence Genetics	Defect	Clinical Symptoms (untreated)	Screening Method	Normal Values	Goals of Screening	Pitfalls of Screening
Fatty Acid Oxidation Disorders AR Screening: 2004	Accumulation of fatty acids and a decrease in cell energy metabolism due to an enzyme defect in the fatty acid metabolic pathway (use of dietary and stored fat)	During the first crisis children have presented with metabolic acidosis, persistent vomiting, hypoglycemia, lethargy, apnea, encephalopathy, coma, cardiopulmonary arrest, or sudden unexplained death.	Elevated metabolites using MS/MS related to specific disorder.	Dependent on specific disorder.	Identify all infants with elevated metabolite levels. Assess need for diet and cofactor therapy and begin immediately	Confirmation may require analysis of urine organic acid, blood Acyl carnitine profile and DNA studies